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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,397	10/02/2000	Lars Eric Sundstrom	MAR37P-314	9763

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	16

DATE MAILED: 10/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,397	SUNDSTROM ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *3,4,7 and 9-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,8 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 14 (filed 7/24/02), claims 1, 19, 23 have been amended.

Claims 3, 4, 7, 9-18 remain withdrawn from consideration, pursuant to the restriction.

Claims 1, 2, 5, 6, 8, 19-24 are examined in this Office action.

Applicants' arguments filed 7/24/02 have been considered and found persuasive in part.

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Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Each of claims 19 and 23 is drawn to a composition. However, a composition must have at least two separate components; a compound *per se* is not a composition. If the claimed composition is intended to contain the compound of formula I in combination with a carrier, this should be so indicated.

- The claims are indefinite as to what is meant by "substantially pure". If the compound is present in a mixture, and constitutes only 50% of that mixture, is it "substantially pure"...?

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947).

As indicated previously, Cherksey teaches (cols 9-10) compound "R". The reference also teaches (col 14, line 62) pharmaceutical compositions. Cherksey does not disclose that the chiral center must be of the "L" configuration.

In response to this rejection, applicants have argued that Cherksey does not teach "substantially pure compounds". It is true that Cherksey does not employ the term "substantially pure" to describe the compounds. However, when a reference discloses the structure of a given compound, and does not also disclose that other impurities are present, then the compound is pure. One could perhaps draw a contrast. Suppose that a biochemist isolated a mixture of proteins from a given animal source, and further disclosed (a) that the proteins in the mixture exhibited a molecular weight range of 10-15 kD, and (b) that the proteins in the mixture stimulated growth of a certain type of cells. The

biochemist could put this information into a claim, and claim a "substantially pure" protein which is isolated by the disclosed method, and which exhibits the indicated properties. But if a biochemist were to claim a protein having a specific amino acid sequence, then the issue of "substantially pure" would be rendered moot. When one opens up the Merck Index, for example, to any page on which a specific structure is disclosed, the formula is that of the pure compound, and not that of a "substantially pure" compound. Similarly, the structures disclosed in Cherksey are those of pure compounds. On the other hand, suppose that compound "X" is known in the prior art, and a given applicant is claiming a mixture of "X" and "Y". Such a mixture may or may not be novel, depending on what "Y" is. In the instant case, applicants have not specified any impurities. Thus, the question here is, would the synthetic organic chemist of ordinary skill recognize that chemical reactions produce impurities? The reality is that dealing with impurities is a daily struggle for the synthetic organic chemist. Of all the things that are obvious to the synthetic organic chemist, none is more obvious than the fact that chemical reactions produce impurities. The term "substantially pure" would encompass the case where the compound is 99.99999999999% pure, as well as the case in which the compound is only about 95% pure.

Applicants have also argued that the disclosure of Cherksey is non-enabling with respect to preparation of the claimed compounds. It is agreed that Cherksey is somewhat short on specifics with regard to preparation methods. However, the instant claims are drawn to

compounds, not to a method of making them. Even if it were true that Cherksey is non-enabling with respect to preparation of the disclosed compounds (and this point is not conceded), it would not follow therefrom that Cherksey is non-enabling with respect to disclosure of compounds *per se*. Furthermore, since Cherksey does not teach that the compounds should be combined with impurities, it may be assumed that the disclosure is that of the pure compounds.

Next, applicants have pointed to the declaration filed 1/23/02, wherein Lars Sundstrom asserts the following:

> "...the methods described in WO 93/12777 were reprocduced exactly in an attempt to synthesize arginine- spermidine and lysine-spermidine... ... the mass spectrometry results for the products ... do not show any trace of arginine- spermidine or lysine-spermidine".

Applicants have declined to state what their reaction conditions were, but the reaction conditions could not possibly have been the same as those used by Cherksey, because Cherksey does not disclose them. Thus, all that applicants have done is to search for, and find, conditions under which two compounds (two compounds which applicants have not yet identified) will not react.

The questions remain. What were the exact starting compounds used in the reaction? What solvent was used? What was the temperature of the reaction? What other reagents, if any, were present? What was the stoichiometry of the reactants and the reagents? What was the length of the reaction? The fact of the matter is that this information is

not diclosed in Cherksey. Thus, it is entirely inadequate to merely say that somewhere in USP 5,242,947 one can find the answers to these questions.

Applicants have cited *In re Williams* (80 USPQ 150). This application was filed as application 431,531 ("effective" file date 4/3/39) which is now USP 2,465,303. The claim under appeal was drawn to the compound L-α-hydroxy-β, β-dimethyl-γ- butyrolactone, and the issue was whether this compound (the "L" enantiomer) was patentable over a disclosure of α-hydroxy-β, β-dimethyl-γ- butyrolactone. The PTO solicitor had argued that the compound of the prior art was a racemic mixture, and that methods of resolving enantiomers were known at the time. The Court found that there was no evidence that those references published before 4/3/39 had disclosed a racemic mixture, and that therefore resolution of that mixture could not have been obvious.

In the instant case, either stereoisomer can be readily synthesized. One would either start with the D-isomer of arginine, or the L-isomer. One has no choice but to make a deliberate decision on this matter before proceding with the synthesis. In the vast majority of cases, peptides containing "L" configurations are more active than, or at least as active as the corresponding "D" isomers. Morever, the convention in peptide chemistry is that the stereochemistry of alpha-carbons of amino acids is of the "L" configuration unless indicated otherwise. Thus, the peptide biochemist of ordinary skill would have expected that L-isomers were intended, but in any case both the D- and the L-isomers would have been

obvious to the skilled peptide chemist.

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Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947) in view of Bodansky (*Int J Pept Prot Res* **25**, 449-474, 1985).

The teachings of Cherksey were indicated previously. Bodansky is cited as showing the state of the art of peptide synthesis (at least in 1985).

An organic chemist of ordinary skill would recognize that an optimal yield would be obtained if there were just one electrophile (the carboxyl group or active ester thereof) and one nucleophile (the amine reactant). One option for a synthetic scheme is as follows (wherein P1 represents a guanidino protecting group, and P2, P3 and P4 represent amino protecting groups):

$P^1NH(C=NH)NH\text{-}(CH_2)_3\text{-}CH(NHP^2)COOH + H_2N\text{-}(CH_2)_3\text{-}N(P^3)\text{-}(CH_2)_4\text{-}NHP^4 \rightarrow$

$P^1NH(C=NH)NH\text{-}(CH_2)_3\text{-}CH(NHP^2)CONH\text{-}(CH_2)_3\text{-}N(P^3)\text{-}(CH_2)_4\text{-}NHP^4 \rightarrow$

$H_2N(C=NH)NH\text{-}(CH_2)_3\text{-}CH(NH_2)CONH\text{-}(CH_2)_3\text{-}NH\text{-}(CH_2)_4\text{-}NH_2$

Certainly, protecting groups for arginine were well known by the 1960's. Moreover, it is not apparent that there would be any need for orthogonal protecting groups to protect the three non-participating amino groups. Once in possession of di-protected spermidine (e.g., with Fmoc groups), the coupling reaction is very straightforward. There are, of

course other synthetic possibilities. The point is that, once presented with the structure of the "target" compound, the organic chemist of ordinary skill could obtain the compound within the bounds of routine experimentation.

Thus, the claims are rendered obvious.

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Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947).

This ground of rejection is predicated on the stipulation that Cherksey failed to optimize reaction conditions, but that the chemist of ordinary skill is nonetheless undeterred by this, and would purify the compounds that are prepared by the methods disclosed in the reference.

In response to this, applicants have argued that the organic chemist of ordinary skill would not have had motivation to use HPLC. However, the organic chemist of ordinary skill would have had motivation to purify compounds produced in a given reaction, if that chemist determined that such impurities were present. Thus, the motivation is present. Although applicants have not mentioned the declaration of Lars Sundstrom in response to this ground of rejection, it appears that applicants believe that the organic chemist of ordinary skill, upon being presented with the structures disclosed in Cherksey, and the other information disclosed in Cherksey, would be unable to produce any reaction products. However, this is simply not true. If a person with absolutely not scientific training were to combine an

aliphatic amine with a carboxylic acid in the presence of a coupling reagent, he could not help but consume starting materials, and produce at least one product.

Thus, the claims are rendered obvious.

*

Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947) in view of the Aldrich Catalog, 1992-1993 edition.

The teachings of Cherksey were indicated previously. The reference does not explicitly recite that compound ("R") shown in column 9 was synthesized starting with L-Arginine, rather than D-Arginine. The Adrich Catalog (1992-1993 edition) lists both stereoisomers of arginine. The D-isomer is available only in a 1 gram bottle; the catalog number is 85,853-6, and the price is $25.00 for the 1 gram. By contrast, the price of a 25 g bottle of L-Arginine is $ 5.70 and for a 100 g bottle the price is $14.45. Clearly, the L-isomer is much less expensive.

The peptide biochemist of ordinary skill is aware that in the vast majority of peptides thus far documented, biological activity is usually greater for the all-L isomer than for the corresponding peptide in which one or more L-isomers have been replaced with D-isomers. However, in the event that applicants are not willing to stipulate that the peptide biochemist of ordinary skill is aware of this, there is another basis for obviousness, which is simply that the L-isomer is less expensive to produce.

Thus, the claims are rendered obvious.

*

Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947) in view of Eldefrawi (*Proc. Natl. Acad. Sci. U. S. A.* 85(13), 4910-13, 1988).

The teachings of Cherksey were indicated previously. Cherksey also teaches (col 13, line 49+) that the procedures disclosed in Eldefrawi may be used. Eldefrawi discloses (p. 4912, col 1) that compound 9 was reacted with compound 6 to produce compound 2. Eldefrawi does not disclose any of the claimed compounds.

The claims are drawn to compounds (and compositions), and not to methods of synthesizing those compounds. However, applicants have made an issue of the synthetic procedures that may have been followed. The point is that Eldefrawi discloses reaction of a polyamine with an active ester of a protected amino acid, wherein all but one of the amino groups of the polyamine is protected. The synthetic chemist of ordinary skill would have taken from this the following reaction scheme (wherein P1 represents a guanidino protecting group, and P2, P3 and P4 represent amino protecting groups):

$$P^1NH(C{=}NH)NH\text{-}(CH_2)_3\text{-}CH(NHP^2)COOH + H_2N\text{-}(CH_2)_3\text{-}N(P^3)\text{-}(CH_2)_4\text{-}NHP^4 \rightarrow$$

$$P^1NH(C{=}NH)NH\text{-}(CH_2)_3\text{-}CH(NHP^2)CONH\text{-}(CH_2)_3\text{-}N(P^3)\text{-}(CH_2)_4\text{-}NHP^4 \rightarrow$$

$H_2N(C=NH)NH\text{-}(CH_2)_3\text{-}CH(NH_2)CONH\text{-}(CH_2)_3\text{-}NH\text{-}(CH_2)_4\text{-}NH_2$

Cherksey thus provides a specific suggestion to employ the procedures disclosed in Eldefrawi. If a synthetic organic chemist of ordinary skill were presented with the "target" compound (Cherksey), together with a suggestion to use the procedures disclosed in Eldefrawi, he would have had no difficulty in obtaining the target compound.

Thus, the claims are rendered obvious.

*

Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947) in view of Hashimoto (*Tetrahedron Lett.* **28**(30), 3511-14, 1987).

The teachings of Cherksey were indicated previously. Cherksey also teaches (col 13, line 50+) that the procedures disclosed in Hashimoto may be used. Hashimoto discloses that compound 5 was reacted with spermine to produce compound 4. Hashimoto does not disclose any of the claimed compounds.

Although the instant claims are drawn to compounds, rather than to a method of synthesizing them, applicants have argued that the disclosure of Cherksey is non-enabling, i.e., fails to provide sufficient information to the skilled organic chemist to synthesize the claimed compounds. Even if this were true for Cherksey taken by itself, it is not true for

Cherksey taken in view of Hashimoto.

Thus, the claims are rendered obvious.

✺

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.